

THE SCIENTIFIC BASIS OF HEALTHRHYTHMS' TECHNOLOGY

AN ANNOTATED BIBLIOGRAPHY OF THE SOCIAL RHYTHM REGULATION THEORY AND ITS VALIDATION

Ehlers, C.L., Frank, E. and Kupfer, D.J. Social zeitgebers and biological rhythms: A unified approach to understanding the etiology of depression. Archives of General Psychiatry, **45**: 948-952, 1988.

In this paper, we posited the theory that stressful life events such as divorce, job loss, death of a partner, etc. were implicated in the onset of depression not only via their psychological meaning, but via the extent to which they resulted in the loss of the social zeitgebers (time cues or normal routines) in a person's life which, in turn, disrupted their biological rhythms and thereby produced many of the symptoms of the depressive syndrome.

Ehlers, C.L., Kupfer, D.J., Frank, E., and Monk, T.H. Biological rhythms and depression: The role of zeitgebers and zeitstörers. Depression, **1**:285-293, 1993.

This follow-up to our 1988 paper added the idea that certain life events, such as presence of a newborn in the home, a change in a child's school schedule, or the need to travel across time zones for business or family events also affected a person's routine in a manner that disrupted their normal biological rhythms.

Monk, T.H., Flaherty, J.F., Frank, E., Hoskinson, K., and Kupfer, D.J. The Social Rhythm Metric (SRM): An instrument to quantify the daily rhythms of life. Journal of Nervous and Mental Disease, **178**:120-126, 1990.

In order to test our social rhythm regulation theory, we developed and validated a self-report instrument to measure the rhythms of people's lives.

Frank, E., Kupfer, D.J., Ehlers, C.L., Monk, T.H., Cornes, C., Carter, S., and Frankel, D. Interpersonal and Social Rhythm Therapy for Bipolar Disorder: Integrating Interpersonal and Behavioral Approaches. Behavior Therapist, **17**:143-149, 1994.

This paper represented the first description of a behavior therapy approach to helping patients to achieve more regular daily routines or social rhythms with the intent of improving their mental health.

Malkoff-Schwartz, S., Frank, E., Anderson, B., Sherrill, J.T., Siegel, L., Patterson, D., and Kupfer, D.J. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: A Preliminary Investigation. Archives of General Psychiatry, **55**(8): 702-707, 1998.

Malkoff-Schwartz, S., Frank, E., Anderson, B.P., Hlastala, S.A., Luther, J.F., Sherrill, J.T., Houck, P.R. and Kupfer, D.J. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. Psychological Medicine, **30**:1005-1016, 2000.

In these two experiments, we used a very rigorous, labor intensive and blinded method to determine the extent to which life events experienced in the period immediately prior to the onset of an episode of depression or mania were characterized by disruption in patients' social rhythms. We demonstrated that such disruptions were even more strongly associated with new onsets of illness than events characterized by psychological stress. This was especially true for new onsets of mania.

Frank, E., Kupfer, D.J., Thase, M.E., Mallinger, A.G., Swartz, H., Fagiolini, A.M., Grochocinski, V., Houck, P., Scott, J., Thompson, W. and Monk, T. Two year outcomes for interpersonal and social rhythm therapy in

individuals with bipolar I disorder. Archives of General Psychiatry, 62:996-1004, 2005.

This paper reported on the results of a randomized trial comparing our behavioral approach to helping patients achieve more regular daily routines (interpersonal and social rhythm therapy - IPSRT) plus medication to clinic visits plus medication as both acute and maintenance treatments for patients with bipolar disorder. We demonstrated that receiving IPSRT during the acute treatment phase was associated with significantly longer periods without a new episode of depression or mania in the subsequent two years. Equally important to our conceptual model, we demonstrated that it was precisely those patients whose daily routines became most regular who received the most benefit from the treatment.

Frank, E., Soreca, I., Swartz, H.A., Fagiolini, A.M., Mallinger, A.G., Thase, M.E., Grochocinski, V.J., Houck, P.R. and Kupfer, D.J. Interpersonal and social rhythm therapy improves occupational functioning in patients with bipolar I disorder. American Journal of Psychiatry, 165:1559-1565, 2008

Here we demonstrated that our behavioral approach to routine regularity not only helped in symptom reduction and prevention of new episodes of illness, but also improved patients' occupational functioning, a major issue for individuals with bipolar disorder.

Swartz, H.A., Frank, E., O'Toole, K., Newman, N., Kiderman, H., Carlson, S., Fink, J.W., Cheng, Y., Maihoefer, C., Wells, K.F., Houck, P.R., Painter, T., Ortenzio, S.H., Simon, S.L., Henschke, P. and Ghinassi, F. Implementing interpersonal and social rhythm therapy for mood disorders across a continuum of care. Psychiatric Services, 62:1377-1380, 2011

This report focused on the feasibility of our behavioral approach to increasing routine regularity across the continuum of psychiatric care from inpatient settings to day hospital and intensive outpatient settings to standard outpatient group and individual treatment in a major inner-city psychiatric hospital. Included in this roll out was an intensive outpatient program devoted to older individuals (65+) with depression.

Corruble, E., Frank, E., Gressier, F., Courtet, P., Bayle, F., Llorca, P.M., Vaiva, G. and Gorwood, P. Morningness-eveningness and treatment response in major depressive disorder. Chronobiology International, 31: 283-9, 2014

This study, conducted in France, demonstrated the relevance of chronotype to treatment response in depression.

Abdullah, S., Matthews, M., Murnane, E. L. Gay, G. and Choudury, T. Towards circadian computing: "Early to Bed and Early to Rise" makes some of us unhealthy and sleep deprived. Ubicomp '14, September 13-17, Seattle, WA, USA.

This report demonstrated that phone usage patterns can be used to detect and predict individual variations indicative of temporal preference, sleep duration and sleep deprivation.

This paper provided the original validation of our sleep algorithm and our assessment of chronotype from passively monitored data. As we have gathered more labelled data from our depression RCT (Frank et al, Frontiers in Digital Health, 4, 2022), from an insomnia RCT (1R44 AA 028164) that is currently in progress and from our deployments in pharmaceutical company studies, we have continued to improve those algorithms using machine learning modeling.

Frank, E., Benabou, M., Bentzley, B., Bianchi, M., Goldstein, T., Konopka, G., Maywood, L., Pritchett, D.,

Sheaves, B. and Thomas, J. What makes a good homeostat? Influencing circadian and sleep-wake regulation for prevention and intervention in mood and anxiety disorders. *Ann N Y Acad Sci.* 2014 Dec; 1334: 1–25.

This paper summarizes the conclusions of a multi-day international conference, chaired by Dr. Frank, focused on understanding the role of circadian and sleep-wake regulation in relation to the course of mood and anxiety disorders. The data presented points to the clear relevance of these factors to our understanding these disorders.

Abdullah, S., Matthews, M., Frank, E., Doherty, G., Gay, G. and Choudhury, T. Automatic detection of social rhythms in bipolar disorder. *Journal of the American Medical Informatics Association*, 2016.

Mathews, M., Abdullah, S., Murnane, E.L., Volda, S., Choudhury, T. and Frank, E. Development and evaluation of a smartphone-based measure of social rhythms for bipolar disorder. *Assessment*. 2016.

Among the first demonstrations of the value of HealthRhythms' technology, these two papers demonstrated that we could detect individual's social rhythms from the sensors on the smartphone, obviating the need for burdensome self-reporting on patients' part.

These papers represent the validation of our 'routine' inference. Again, as we have gathered more labelled data from our depression RCT (Frank et al, 2022), from an insomnia RCT (1R44 AA 028164) that is currently in progress, and from our deployments in pharmaceutical company studies, we have continued to improve those algorithms using machine learning modeling.

Goldstein, T.R., Merranko, J., Krantz, M., Franzen, P., Levenson, J., Axleson, D., Birmaher, B., and Frank E. Early Intervention for Adolescents At-Risk for Bipolar Disorder: A Pilot Randomized Trial of Interpersonal and Social Rhythm Therapy (IPSRT), *Journal of Affective Disorders*, 235: 348-356. (2018)

Here we showed the possible value of the social rhythm approach in preventing the initial onset of bipolar disorder in adolescents with a family history of bipolar disorder.

Frank, E., Wallace, M., Matthews, M.J., Kendrick, J., Leach, J., Moore, T., Aranovich, G., Choudhury, T., Shah, N.R., Framroze, Z., Posey, G., Burgess, S., Kupfer, D.J. Precision digital intervention for depression based on social rhythm principles adds significantly to outpatient treatment. *Frontiers in Digital Health*, 4 , 2022. <https://www.frontiersin.org/articles/10.3389/fdgth.2022.870522>

This 16-week randomized controlled trial demonstrated the efficacy of Cue, our digital intervention platform for depression, plus standard-of-care outpatient psychiatric treatment, consisting primarily of antidepressant pharmacotherapy when compared to standard-of-care treatment plus digital monitoring alone. Outpatients who received Cue improved twice as much as those receiving standard care only.

Wallace, M. Frank, E, et al. Could psychiatry have its own vital signs? A preliminary proof of concept. Under review.

This paper examines whether passively sensed behavioral data acquired from commercial smartphones could constitute objective vital signs for psychiatric disorders in much the way that pulse rate, temperature, respiration rate, and blood pressure constitute vital signs in physical medicine. Working from the social zeitgeber conceptual model, we collected continuous behavioral data from 131 psychiatric outpatients with a lifetime diagnosis of either depression and/or an anxiety disorder for a period of 16 weeks. We found that irregularity of sleep end time over the study period was significantly related to higher mean self-reported

depression level ($p = 0.02$). Lower mean total step count ($p=0.04$) and lower mean walking rate ($p=0.02$) in the prior week were both significantly associated with higher depression scores. Indices of greater recent social engagement (mean location entropy, $p = 0.02$; distances traveled $p=0.02$) in the past week predicted higher PHQ-8 scores, and less regularity in social engagement over the 16 weeks was associated with higher depression severity ($p=0.02$). These initial results suggest that the commercial smartphone may provide a practical way of obtaining continuous, objective behavioral measurements which could be considered the kind of vital signs that have proven invaluable to assessment and treatment decision-making in physical medicine.